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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,468	02/08/2002	Stephen J. Benkovic	P05537US1	9968

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EXAMINER

SWOPE, SHERIDAN

ART UNIT PAPER NUMBER

1652

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/071,468	Applicant(s) BENKOVIC ET AL.	
	Examiner Sheridan L. Swope	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on December 23, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 and 14-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 14-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response, on December 23, 2003 to the First Action on the Merits of this case is acknowledged. It is acknowledged that applicants have cancelled Claims 8-13, amended Claims 1, 5, and 6, and added new Claims, 14-29. Claims 1-7 and 14-29, which are encompassed by the elected invention, are pending. Claims 1-7 are hereby reconsidered and Claims 14-29 are hereby considered on their Merits

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 15, 17, 20, 21, 23-26, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is rejected for being redundant with Claim 4.

Claim 20 is rejected for being redundant with Claim 17.

Claim 23 is rejected for being redundant with Claim 18.

Claim 24 is rejected for being redundant with Claim 19.

In Claim 14, the phrase on line 3 "fused to protease followed by" is confusing, as the protease is not a fusion protein. Correction is required. For purposes of examination, it is assumed that said phrase is meant to be: "fused to a protease substrate sequence followed by".

In Claims 1 and 14 the phrase on line 5 "a protease" should be amended to "said protease". Correction is required.

Art Unit: 1652

In Claims 20 and 25 the phrase on line 7-8 “of protease acitivity” should be amended to “of said protease activity”. Correction is required.

In Claim 15, the phrase on line 2 “of the serine substrate” is confusing, as it is unclear what is meant by “serine substrate”. Correction is required. For purposes of examination, it is assumed that said phrase is meant to be: “of the serine protease substrate sequence”.

In Claim 15, the phrase on line 2 “of the serine protease substrate” has no antecedent basis. Correction is required. For purposes of examination, it is assumed that Claim 15 is meant to depend from Claim 16.

In Claims 17, 23, and 28, each on line 1, the phrase “the protease sequence” has no antecedent basis. Correction is required. For purposes of examination, it is assumed that said phrase is meant to be: “the protease”.

In Claim 20, lines 3-4, and Claim 25, lines 3-4, the phrase “fused to serine protease sequence that encodes a serine protease” is confusing, as the protease is not a fusion protein. Correction is required. For purposes of examination, it is assumed that said phrase is meant to be: “fused to serine protease substrate sequence that encodes a serine protease substrate”.

In Claim 20, line 6, Claim 21, line 2, Claim 25, line 6, and Claim 26, line 2, the phrase “the serine substrate” is confusing, as there is no such thing as a “serine substrate” for proteases. Correction is required. For purposes of examination, it is assumed that said phrase is meant to be: “the serine protease substrate”.

In Claim 25, line 7, the phrase “purifying the serine protease substrate” is unclear. It is unclear whether what is purified is the whole fusion protein comprising the substrate sequence,

Art Unit: 1652

just the substrate sequence, or both. For purposes of examination, it is assumed that only the fusion protein comprising the substrate sequence is purified.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of Claims 1-3, 5, and 6 under 35 U.S.C. 112, first paragraph, for lack of enablement, is maintained. As stated in the prior action, Claims 1-3, 5, and 6 are so broad as to encompass a method using a fluorescent protease substrate comprised of an N-terminal portion of any fluorescent reporter fused to a protease substrate motif followed by the C-terminal portion of the reporter. In support of their request for withdrawal of said rejection, Applicants provide the following arguments. "Other fluorescent proteins are presently known in the art such that one of skill could create a construct having a fluorescent reporter other than GFP following the teachings of the specification. Moreover, having knowledge of the information taught in the specification, it would be reasonable for a skilled artisan to check known sources, in existence and known at the time of filing of the application, such that it would be no more than routine optimization to create a construct having a fluorescent protein that is a functional equivalent of the GFP."

Said argument is not persuasive. The specification does not support the broad scope of Claims 1-3, 5, and 6 because the specification does not establish any fluorescent proteins, other than GFP, that can be used to prepare a fluorescent protease substrate reporter. Furthermore, the specification does not disclose where in any fluorescent protein, other than GFP, the substrate

Art Unit: 1652

sequence can be inserted with an expectation of successfully producing a fluorescent protease substrate reporter. To determine which fluorescent proteins and where in said proteins the protease substrate can be successfully inserted would require undue experimentation as, the specification fails to provide sufficient guidance to enable one of skill in the art to make and use the full scope of the recited invention.

Rejection of Claims 1-3, 5, and 6 under 35 U.S.C. 112, first paragraph, for insufficient structural written description, is maintained. The specification fails to sufficiently describe the structural aspects of the genus of fluorescent protease substrates comprised of an N-terminal portion of any fluorescent reporter fused to any protease substrate motif followed by the C-terminal portion of the reporter to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In support of their request for withdrawal of said rejection, Applicants provide the following arguments: "The specification discloses that the protease substrate must be susceptible to protease activity and when cleaved has little intrinsic affinity to the fluorescent protein." Said argument is irrelevant, as it does not address the lack of structural written description in the specification. Therefore, rejection of Claims 1-3, 5, and 6 under 35 U.S.C. 112, first paragraph, for insufficient structural written description, is maintained. New Claims, 14-29, are rejected under 35 U.S.C. 112, first paragraph, for insufficient structural written description, for the same reasons.

Claims 25-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification. Claims 25-29 recite a method in which a fluorescent protease

Art Unit: 1652

substrate is expressed in a cell in the presence of a protease, the substrate is then purified, and a change in the fluorescence of the purified substrate is measured. The specification fails to disclose said method and recitation of said method in Claims 25-29 is deemed New Matter. Therefore, Claims 25-29 are rejected under 35 U.S.C. 112, first paragraph, because they contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of Claims 1-7 under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 (in IDS) in view of Abedi et al, 1998 is maintained. New Claims 14 and 15 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 (in IDS) in view of Abedi et al, 1998. In support of their request for withdrawal of said rejection, Applicants provide the following arguments. "There is no suggestion in the prior art represented by such references that they be combined in the manner proposed by the Examiner. Mahajan fails to teach detecting protease activity by the quenching of the fluorescent [fluorescence]... instead, Mahajan teaches that upon cleavage of bifs and bYFs there is a decrease in the fluorescence resonance energy transfer (FRET)... Applicants teach that the quenching is measured by means such as fluorescent activated cell sorting (FACS), which is different from FRET. Abedi fails to

Art Unit: 1652

teach detecting the quenching in fluorescence as a result of proteolytic activity being present. In fact, Abedi teaches away from the Applicants' method... 'in certain cases that may be helpful to select from the expression library those sequences that express the highest level of fusion protein as cells.'".

These arguments are not found to be persuasive. The use of FACS as a means to measure changes in fluorescence is not recited in the instant claims. In fact, as stated by the Applicants, a loss of FRET is a loss in fluorescence (pg 2, lines 3-4) and any means to measure a loss of fluorescence is encompassed by the instant claims. Furthermore, Applicants have merely pointed out those aspects of the instant invention that are missing from each reference and have failed to acknowledge that those missing aspects are provided by the complementary reference. This is a 35 U.S.C. 103(a) rejection, not a 35 U.S.C. 102 rejection. Although Mahajan does not teach assaying protease activity using the technique of FACS, Abedi, et al does. Abedi fails to teach the quenching of fluorescence as a result of proteolytic activity; however, Mahajan does. It would be obvious to a person of ordinary skill in the art to combine those aspects of Mahajan (a fluorescent fusion protein for measuring protease activity) and Abedi (a fluorescent fusion protein comprised of GFP and a protease substrate motif) to make the instant invention. One would be motivated to do so because, as described in the prior action, the GFP-substrate fusion protein would be smaller than the CFP-peptide-GFP fluorescent substrate taught by Mahajan et al and the GFP-substrate fusion protein would avoid bleed-through background fluorescence, which would occur upon cleavage of the fluorescent substrate taught by Mahajan et al. Therefore, rejection of Claims 1-7 under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998 is maintained and new Claims 14 and 15 are also rejected

Art Unit: 1652

under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998.

Claims 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998 and further in view of Martin et al, 1997. The teachings of Mahajan et al and Abedi et al are described above. Mahajan et al do not teach analysis of serine protease activity. However, serine proteases, including the NS3/4A protease, were well known in the art. It would have been obvious to a person of ordinary skill in the art to use the method devised from combining of Mahajan et al and Abedi et al, as described above, to analyze the activity of serine proteases. Motivation to do so is provided by the desire to test for inhibitors of serine protease activity. For example, Martin et al teach that, designing inhibitors of NS3/4A, a hepatitis C virus serine protease, as a means to develop anti-viral agents is a desirable and practical objective (Abstract). Martin et al further disclose a peptide substrate that is useful for measuring NS3/4A activity (pg 609, lines 2-3). The expectation of success is high as fluorescent fusion protease substrates as well as a peptide substrate for the serine protease NS3/4A are known in the art. Therefore, Claims 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998 and further in view of Martin et al, 1997.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

Art Unit: 1652

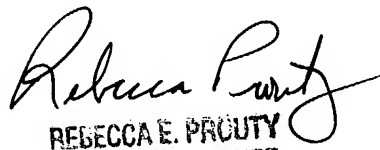
MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.


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